



# Histamine Type 2 Receptor Antagonists as Adjuvant Treatment for Resected Colorectal Cancer

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## Objective

To assess whether histamine type 2 receptor antagonists (H<sub>2</sub>RAs) improve overall survival when used as pre-, peri-, or postoperative therapy in patients with colorectal cancer who had surgical resection with curative intent.

## Type of Review

A review of six randomized, controlled trials (RCTs) to assess the outcome of an intervention on overall survival.

## Relevance for Nursing

Colorectal cancer is the third most commonly diagnosed cancer in the world. Surgical resection is the main treatment strategy for colorectal cancer; however, chances of postsurgical relapse exist because of the undetected spread of cancer cells from the primary tumor to other tissues. In general, metastatic colorectal cancer is not curable. Therefore, adjuvant therapies that target remaining cancer cells are administered around the time of surgery to improve patient outcomes.

H<sub>2</sub>RAs, including ranitidine and cimetidine, bind to cognate H<sub>2</sub> receptors and block the action of histamine. H<sub>2</sub>RAs block H<sub>2</sub> receptors that also are present on other cells types, mediating processes that have been investigated for their anticancer effects. Histamine acts as a growth factor for some gastrointestinal cancer cell lines, and inhibition of histamine activity through H<sub>2</sub>RAs has been shown to reduce colon cancer cell proliferation. H<sub>2</sub>RAs also have immunologic effects that collectively act to increase immune function. In addition, cimetidine has been shown to inhibit adhesion of metastatic cancer cells to healthy endothelial cells in a dose-

dependent manner. Therefore, H<sub>2</sub>RAs, particularly cimetidine, may be suitable for use as adjuvant therapies delivered around the time of surgery to simultaneously stimulate patients' immune function, reduce cancer cell proliferation and spread, and potentially improve patients' outcomes. A systematic review of the effect of H<sub>2</sub>RA use as an adjuvant therapy for the treatment of colorectal cancer was warranted. As nurses play vital roles in the care of patients undergoing treatment for cancer, maintaining up-to-date knowledge of available therapies is beneficial for providing comprehensive patient care.

## Characteristics of the Evidence

This review included six RCTs involving 1,229 participants of any age, gender, or disease stage (excluding metastatic disease) with colorectal cancer who had undergone curative resection. Meta-analysis was performed using data from 981 patients. Interventions included H<sub>2</sub>RAs used around the time of surgery, for any duration, and at any dose or method of delivery. The mean follow-up time was 2.5 years, varying from 1.2–10.7 years among the six studies. Three of the studies compared H<sub>2</sub>RA treatment groups to placebo and the other three compared H<sub>2</sub>RA treatment to no treatment. Cimetidine was used in five of the included studies; one study used ranitidine. H<sub>2</sub>RAs could be used

in conjunction with other nonsurgical treatments provided that H<sub>2</sub>RA use was the only variable between treatment and control groups. The primary outcome measured was overall survival, and no secondary outcomes were examined. Three studies were at high risk for performance and detection bias because of the lack of a placebo control, and one study also was at high risk for reporting bias because the statistical analyses used in the report differed from analyses described in the protocol. The risk of selection bias was either low or, for three of the studies, unclear because the methods used for randomization lacked description.

## Summary of Key Evidence

The results of the meta-analysis showed an overall trend of improved patient survival with H<sub>2</sub>RA use around the time of surgery; however, the effect was not statistically significant when all six studies were combined. The largest trial (N = 560) included in the meta-analysis used ranitidine and showed the least effect on overall survival. The other five studies (N = 421) investigated the effect of cimetidine and demonstrated a statistically significant increase in overall survival with the use of cimetidine as an adjuvant therapy for the treatment of nonmetastatic colorectal cancer (hazard ratio = 0.53; 95% confidence intervals [0.32, 0.87]).

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